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PRINCIPAL INVESTIGATOR: Charnita Zeigler-Johnson, Ph.D., M.P.H.

CONTRACTING ORGANIZATION: Thomas Jefferson University
Philadelphia, PA 19107

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14. ABSTRACT Background: The goal of this pilot study was to examine the relationship between inflammation markers in the tumor microenvironment and PCa outcomes by obesity status. Methods: We selected 75 obese and 75 non-obese patients from the Study of Clinical Outcomes, Risk and Ethnicity. Sufficient paraffin-embedded prostatectomy tissue from 99 patients was available for pathology studies. Tumor samples were cut, deidentified, stained, imaged, and analyzed for cell type and count. We linked T cells and macrophages (TILS) to clinical and demographic data. Statistical analyses included frequency tables, Kruskal-Wallis tests, Spearman correlations, and multivariable models. Results: We observed univariate associations between increased CD68 cells and tumor grade (p=0.019) and biochemical failure (p=0.033). In multivariable analyses, CD3 (HR=0.93, 95% CI= 0.88-0.99) and CD8 counts (HR=1.08, 95% CI=1.01-1.17) were associated with biochemical failure. There were no differences in TILS by obesity. Conclusion: TILS did not differ by obesity status. However, inflammation markers were associated with poor PCa outcomes. Further examination of underlying mechanisms that influence obesity-related effects on PCa outcomes is warranted.					
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1. Introduction

In recent years, there has been a growing interest in the tumor microenvironment as a potential area for investigating the underlying biology of carcinogenesis and metastasis. Inflammation is a key characteristic of cancer that has been associated with disease severity. Under chronic inflammation, T lymphocytes and macrophages in the tumor microenvironment secrete various factors that may increase cell proliferation and inhibit cell death. The presence of tumor infiltrating lymphocytes (TILS) and other inflammatory factors in tumor samples may be indicative of aggressive tumors that are likely to metastasize. Obesity represents a chronic inflammatory environment that sets the stage for cancer progression and poor prognosis, however, it is not clear which mechanisms drive this association in the tumor microenvironment. The goal of this study is to examine prostate cancer (PCa) specimens to characterize differences in TILS within the tumor microenvironment by obesity status and cancer severity. Building upon the infrastructure of an ongoing case-control study at the University of Pennsylvania, the Study of Clinical Outcomes, Risk and Ethnicity (SCORE), this collaborative project sought to address the following specific aims:

Specific Aim 1. To describe the anatomical distribution and composition of tumor infiltrating lymphocytes by obesity comparing 75 normal weight and 75 obese prostate cancer patients

Specific Aim 2. To describe the relationship between inflammation in the tumor microenvironment and prostate cancer outcomes, including prognostic scores and risk of biochemical failure

2. Key Words

Prostate Cancer; Obesity; Tumor Microenvironment; T-cells; Macrophages; Tumor Infiltrating Lymphocytes; Biochemical Failure

3. Accomplishments

3.a. MAJOR GOALS OF THE PROJECT

Statement of Work Year 1

Major Goal 1: To characterize inflammatory cells by obesity.

- IRB approval

- IRB approval was obtained initially July 2013.
- Tissue sample selection
 - Process of selection occurred between PI and pathology group over the course of the study as some samples were determined to be insufficient for the project because of lack of adequate tumor tissue. New samples were selected from a list of patients matched by obesity status and race to provide balance in the ongoing selection process. The selection process was completed in May 2015.
- Review of pathology reports to identify dominant cancer areas
 - Dominant cancer areas of the tumor were used to study the TILs present in each tumor sample. This work was completed after the final samples were selected in spring 2015.
- Staining and cutting of slides
 - Stored paraffin-embedded tumor tissue samples were cut, deidentified, stained, imaged, and analyzed for cell type and count in the Pathology Laboratory at the University of Pennsylvania. Cells for the dominant nodule of prostate cancer were characterized.
- Imaging stains
 - Imaging was completed to observe type and number, of TILs in the tumor samples. Prostate sections from resected glands were stained to identify the presence of TILs (cytokeratin from tumor cells and CD3, CD8, and FoxP3 for T cells; CD68 for macrophages.) The pathology laboratory was unable to complete the characterization of neutrophils as planned in the study proposal. This cell type will be pursued in future investigations.
 - We read 10 high power fields and counted each field for positive cells. Tumor samples were scored for infiltrating lymphocytes by a machine detection system (InForm version 1.0.2, Caliper Life Sciences, Hopkinton, Mass.) Stained slides were scanned at low (40x), and high (400x) magnification using the Vectra imaging system (Vectra version 0.4, Cambridge Research and Instrumentation, Woburn, Mass.). A high-resolution image is

generated for each field of tumor to be scored. Approximately ten representative tumor images were scored for each case. Images were acquired using the multispectral imaging system and converted to optical density space, unmixed to separate spectral components, and annotated for ground truth (tumor, stroma, and background) by a trained pathologist. A tissue segmentation algorithm was then trained to identify areas of tumor and areas of stroma using the combined cytokeratin and hematoxylin information from the unmixed spectral images.

- Next, a cell segmentation algorithm was optimized for the task of identifying TILS. This algorithm finds DAB positive lymphocytes within the tumor areas and allows for counts within the tumor. The tissue and cell segmentation algorithms were applied to the entire set of tumor images in batch mode, producing separate output files for each core. These output files consisted of a segmentation map demonstrating the tissue segmentation and cell segmentation (regions identified as lymphocytes.)
- The output images were reviewed to eliminate images that do not show good tissue segmentation as judged by our pathologist. The good images are then used for scoring counts of TILS within each compartment. This work was completed in summer 2015.
- Milestone: Completion of Pathology Dataset
 - The pathology dataset for the SCORE subset was completed summer 2015. The dataset was then merged with the epidemiological dataset of SCORE, including both demographic and clinical variables.

Major Goal 2: To describe the relationship between inflammation and prognostic scores and biochemical failure.

- Prospective and retrospective data collection
 - Updating of the database for the Study of Clinical Outcomes, Risk and Ethnicity (SCORE) at the University of Pennsylvania was supervised by Dr. Zeigler-Johnson. Medical record reviews involved collection of retrospective (pathology and clinical data at the time of diagnosis) and prospective (biochemical failure) data.

The work for SCORE is ongoing, but was completed for this project in summer 2015.

- Data entry
 - Data entry was supervised by Dr. Zeigler-Johnson. New pathology data obtained from this project was entered into the SCORE database in summer 2015.
- Data analysis
 - Data were merged and analyzed by Dr. Zeigler-Johnson and Dr. Morales. Descriptive analyses showed associations between TILS and prostate cancer outcomes, including advanced tumor grade at diagnosis and risk for biochemical failure. Statistical analyses included frequency tables, Kruskal-Wallis tests, Spearman correlations, Generalized Linear Models, Logistic Regression and Cox Regression models.
 - For Aim 1, we applied generalized linear models with a gamma family and log link for CD68, CD3 and CD8. A binary variable indicating the presence of FOXP3 was modeled using logistic regression. The primary risk factor of interest was obese compared to normal weight men. Models were adjusted for age and race. Deviance residuals were examined for model goodness of fit.
 - For Aim 2, the association between biochemical failure and pathological measures was examined using logistic regression. The model included CD3, CD8 and CD68, age, race and grade. FOXP3 was excluded due to missing data. The association between time to biochemical failure and pathological measures was examined using a Cox proportional hazard model with the same predictor variables. A test of the proportional hazards assumption was performed based on the Schoenfeld residuals. This work was completed summer 2015.
- Summarize Findings
 - The tumor samples of 99 SCORE patients were included in the final analysis. Sixty-three were non-obese and 36 were obese. Median age of the sample was 60 (range=42-73.) 18.6% of the sample was African-American and the remaining were Caucasian. Obese and non-obese patients were similar on all demographic and clinical

factors, except obese men were more likely to have diabetes (25% vs. 3%, p=0.001, Table 1.)

Table 1. SCORE Demographics (N=99)

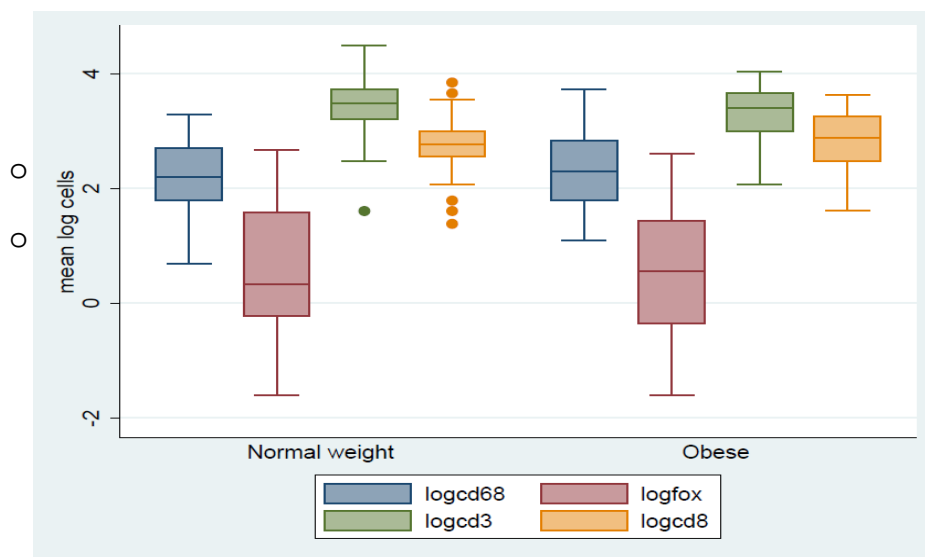
Patient Characteristics		Non-obese (N=63)	Obese (N=36)	p-value
Median Age (years)		61	58	0.065
African American		14.29%	27.78%	0.101
Married		83.6%	83.3%	0.972
Education	<College	39.3%	48.6%	0.652
	College	31.2%	28.6%	
	Post-Graduate Degree	29.5%	22.9%	
Smoking Status	Never	56.9%	42.9%	0.423
	Former	34.5%	45.7%	
	Current	8.6%	11.4%	
Median Body Mass Index (kg/m ²)		23.7	31.9	<0.001
Comorbidity Present		42.9%	52.8%	0.341
	Diabetes	3.2%	25.0%	0.001
Tumor Stage	T3/T4	37.1%	50.0%	0.212
Tumor Grade	≥ 7	46.9%	65.5%	0.112
Follow Up (months)		38	23	0.080
Biochemical Failure		16.4%	31.4%	0.086
Kattan Score		0.05	0.08	0.130

- Aim 1
 - Three T-cells were studied. Overall, the median CD3 cell count was 32 (range=5-90); CD8 cell count was 17 (range 4-47); and FOXP3 cell count was 1 (range 0-15.) The presence of FOXP3 was also evaluated. Overall, FOXP3 cells were present in 75% of tumor samples and absent in the remaining 25%.
 - One macrophage was studied. Overall, median CD68 cell count was 10 (range 0-42.)
 - There were no significant differences in TIL counts by obesity status (Table 2 and Figure 1)

Table 2. Univariate Tumor Infiltrating Lymphocyte (TIL) Count Associations with Obesity Status

TIL		Non-Obese	Obese	p-value
T Cells	CD3	33	30	0.182
	CD8	16	18	0.289
	FOXP3	1	0.8	0.922
	Presence of FOXP3	75.0%	74.1%	0.928
Macrophages	CD68	9	10	0.290

Figure 1. Tumor Infiltrating Lymphocyte Counts by Obesity Status in the SCORE Study



○ Aim 2

- Univariate associations with tumor outcomes were observed for CD68. Greater CD68 cell counts in the tumor were associated with advanced tumor grade ($p=0.019$) and biochemical failure ($p=0.033$, Table 3.)

Table 3. Univariate Associations between TILs and Prostate Cancer Outcomes

TIL		Stage 1/2	Stage 3/4	Grade <7	Grade ≥7	No Failure	Biochemical Failure	Kattan Score
T Cells	CD3	34	30 $P=0.336$	35	30 $P=0.335$	31	32 $P=0.533$	$r=-0.187$
	CD8	16	17 $P=0.251$	15	19 $P=0.207$	16	18 $P=0.264$	$r=0.101$
	FOXP3	0.9	0.8 $P=0.976$	0.4	0.8 $P=0.663$	0.8	0.9 $P=0.610$	$r=-0.097$
	FOXP3 Presence	79%	71% $P=0.434$	67%	68% $P=0.935$	75%	74% $P=0.743$	$P=0.878$
Macrophages	CD68	10	10 $P=0.454$	9	13 $P=0.019$	9	16 $P=0.033$	$r=0.211$
Neutrophils	MPO							

* $p<0.05$

- Additional analyses demonstrated the following univariate and multivariable associations with demographic and clinical factors:
 - Univariately, the presence of FOXP3 was associated with being married vs. unmarried (80% vs. 42%, $p=0.005$)
 - Univariately, CD68 cell counts were greater for African Americans vs. Caucasians (14 vs. 9, $p=0.044$); and CD68 cell counts were

greater for men with higher Gleason score (≥ 7) vs. those with lower Gleason score (13 vs. 9, $p < 0.019$).

- Univariately, CD3 counts were lower for African Americans vs. Caucasians (23 vs. 33, $p = 0.008$); and CD3 counts were lower with higher Kattan score ($r = -0.273$, $p < 0.05$). Multivariable models adjusting for obesity and age also showed that African Americans have lower CD3 counts than African Americans ($p = 0.013$).
 - Multivariable models including age, race, tumor grade, CD3, CD8, and CD68 showed that CD3 and CD8 were associated with time to biochemical failure. A decreased risk of failure was associated with higher CD3 and increased risk of failure with higher CD8.
- Milestone: Prepare abstract/manuscript
 - An abstract describing the results of this project is being prepared for submission to the 2016 American Association of Cancer Research (AACR) meeting in New Orleans, LA (abstract submission due December 1, 2015.) A manuscript and new grant proposal related to this topic will be prepared for submission in the new year.

3.b. ACCOMPLISHMENTS UNDER THESE GOALS

- Major Activities: This study involved laboratory analysis by pathologists and linkage with clinical and epidemiological data to examine the relationships among TILs, obesity and prostate cancer outcomes.
- Specific Objectives: (1) To describe the anatomical distribution (quantity and presence of clustering) and composition (type) of tumor infiltrating lymphocytes, macrophages and neutrophils by obesity comparing 75 normal weight and 75 obese prostate cancer patients; (2) To describe the relationship between inflammation in the tumor microenvironment and prostate cancer outcomes, including prognostic scores and risk of biochemical failure
- SIGNIFICANT RESULTS: Reported in the section 3.a..
- OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT: Nothing to Report.

- RESULTS DISSEMINATED TO COMMUNITIES OF INTEREST: Nothing to Report.
- PLANS FOR NEXT REPORTING PERIOD: Nothing to Report.

4. Impact

4.a. IMPACT ON DEVELOPMENT OF THE PRINCIPAL DISCIPLINES

A causal link between chronic inflammation and cancer has been suspected for many years. Increases in T cells like FOXP3 have been associated with high Prostate Specific Antigen (PSA) levels and carcinogenesis. [1] Under chronic inflammation, there is overproduction of tumor growth factors and new blood vessel formation. A number of complex cellular and cytokine-related events of the inflammatory response may stimulate tumor growth and progression. [2] Pro-inflammatory cytokines including TNF- α , IL-6, TGF- β 1, and C-reactive protein, are produced at greater levels in obese than non-obese subjects. [3] Obesity, therefore, has the potential to change the tumor microenvironment to a pro-inflammatory state.

Little is known about the underlying mechanisms of obesity leading to poor prostate cancer outcomes. Factors, such as tumor infiltrating lymphocytes (TILS), that may affect differences in the tumor microenvironment and promote prostate cancer [4] have not been described by BMI. The goal of this study was to examine if there are differences in tumor microenvironment inflammation by obesity status. This pilot study showed that there are no differences in specific inflammation biomarkers by obesity. This information is critical to helping to advance the scientific investigation beyond tumoral cell type and number to perhaps include cell function (there may be differences in how T-cells and macrophages function by obesity status), or genetic pathways that may alter immunity/inflammation. This information may deepen our knowledge of factors that mediate obesity effects on prostate cancer. The link between BMI and prostate cancer outcomes is complex, with different associations by ethnicity and SES. [5-8] Continued research in this area will guide treatment protocols that may include immunotherapy vs. obesity reduction as they apply to diverse populations. The long-term objective is to be able to suggest ways to improve treatments for men at high risk for poor outcomes by targeting components of the tumor microenvironment. [9]

4.b. IMPACT ON OTHER DISCIPLINES

Because there is heterogeneity within the malignant tumor, describing the inflammatory response during carcinogenesis may provide a more complete understanding of the molecular pathogenesis of the cancer.[10] We proposed to study tumor samples from a diverse patient population and determine if obesity is differentially associated with inflammatory biomarkers. Although we did not find changes by obesity status, we did detect differences by other factors, such as race and cancer progression. The quantification of changes in the tumor microenvironment may provide tumor signatures to improve cancer prognostics that can be applied to other cancers, particularly to identify high risk patients. Genetic pathways that are critical to promoting inflammation may be targeted to improve precision medicine. Other uses for these techniques include the application to other diseases where inflammation may be an underlying biological concern, such as cardiovascular disease.

This pilot project laid a foundation for extending this research to include other BMI groups and other ethnic populations for which inflammatory responses may be more pronounced. **By studying patients reflecting a cross-section of BMIs, we were also able to distinguish factors that increase risk from those that are protective in individuals with different phenotypes.** Research involving patient BMI may suggest new approaches for chronic disease intervention via weight management, physical activity, targeted screening of high risk groups and novel treatments using agents that target inflammation pathways. If patients can be better classified in terms of risk for disease progression, treatments can be tailored to prevent over- or under-treatment of patients.[11]

4.c. IMPACT ON TECHNOLOGY TRANSFER

Nothing to report.

4.d. IMPACT ON SOCIETY BEYOND SCIENCE AND TECHNOLOGY

Nothing to report.

5. Changes/Problems

5.a. CHANGES IN APPROACH

There were no changes made to the protocol. However, there were problems encountered along the way. There were some prostate tissues (34 % of the initial sample) that were not able to be used for the study. The majority of these were obese samples. Although other samples were chosen as replacements

(alternates), not all could be used because of missing data or insufficient stored sample.

5.b. ACTUAL PROBLEMS AND ACTIONS TO RESOLVE THEM

Because of a funding delay resulting from the Primary Investigator's (PI – Zeigler-Johnson) move to Thomas Jefferson University, the official start date of this project was April 1, 2014. Although the PI is a faculty member at Jefferson, she maintains affiliation with the University of Pennsylvania as an adjunct faculty member in the Center for Clinical Epidemiology and Biostatistics.

An extension was recently granted by the Department of Defense to give the pathologists working on this project additional time to complete the reading of samples. Because of clinical constraints and other responsibilities, the pathology staff needed additional time than anticipated to complete the project. Future studies may require 50% effort from a resident or clinical staff for completion of study tasks.

5.c. CHANGES THAT HAD A SIGNIFICANT IMPACT ON EXPENDITURES

None to report.

5.d. SIGNIFICANT CHANGES IN CARE OF HUMAN SUBJECTS, BIOHAZARDS, AND/OR SELECT AGENTS

None to report.

6. Products

Although no products related to TILS have yet been generated, an abstract and manuscript describing the results of this pilot grant are planned for the coming year. In addition to these plans, related products on the topic of obesity and prostate cancer have been distributed during the grant funding cycle.

6.a JOURNAL PUBLICATIONS

Zeigler-Johnson C, Morales KH, Glanz K, Spangler E, Mitchell J, Rebbeck TR: Individual- and neighborhood-level education influences the effect of obesity on prostate cancer treatment failure after prostatectomy. Cancer Causes and Control, 26(9): 1329-1337, 2015.

6.b. BOOKS OR OTHER NON-PERIODICAL, ONE-TIME PUBLICATIONS

Nothing to Report

6.c. OTHER PUBLICATIONS, CONFERENCE PAPERS, AND PRESENTATIONS

Zeigler-Johnson C, Morales K, Glanz K, Spangler E, Mitchell J, Rebbeck TR: Education Discordance and Prostate Cancer Risk Factors. The Science of Global Prostate Cancer Disparities in Black Men Conference, Montego Bay, Jamaica. 2014 Notes: Poster Presentation.

Spangler E, Zeigler-Johnson C, Mitchell J, Rebbeck TR: Diabetes and Prostate Cancer: Clinical Characteristics and Disparity in Outcomes. American Association for Cancer Research Annual Meeting, Philadelphia, PA. 2015. Notes: Poster Presentation.

Zeigler-Johnson C, Morales K, Mitchell J, Spangler E, Glanz K, Rebbeck TR: Modification of Obesity Effects on Prostate Cancer Outcomes by Age and Education. American Association for Cancer Research, Philadelphia, PA. 2015 Notes: Poster Presentation.

6.d. WEBSITES OR INTERNET SITES

Nothing to report.

6.e. TECHNOLOGIES OR TECHNIQUES

Nothing to report.

6.f. INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Nothing to report.

6.g. OTHER PRODUCTS

Nothing to report.

7. Participants and Other Collaborating Organizations

Name:	Charnita Zeigler-Johnson
Project Role:	PI

Researcher Identifier (ORCID ID)	
Nearest Person Month Worked	2
Contributions to Project	Dr. Zeigler-Johnson supervised updating of the epidemiological dataset and provided data management, data analysis, IRB progress reports, and supporting literature reviews for completion of the study. She also conducted matching and selection of the sample population for the study.
Funding Support	
Name:	Knashawn Morales
Project Role:	Biostatistician
Researcher Identifier (ORCID ID)	
Nearest Person Month Worked	1
Contributions to Project	Dr. Morales provided guidance in study design, matching technique, and data analysis. She also conducted multivariable analyses to address aims 1 and 2 of the project, and helped with interpretation of study results.
Funding Support	
Name:	Dr. Michael Feldman
Project Role:	Pathologist
Researcher Identifier (ORCID ID)	
Nearest Person Month Worked	3
Contributions to Project	Dr. Feldman provided leadership and research support in the Pathology Laboratory to complete the pathology analyses for this project. He offered guidance in selection of TILS and planned appropriate laboratory techniques to complement the needs of the study design.
Funding Support	

Name:	Priti Lal
Project Role:	Pathologist
Researcher Identifier (ORCID ID)	
Nearest Person Month Worked	1
Contributions to Project	Dr. Lal completed macrophage analysis for this study.
Funding Support	Pathology Core at the University of Pennsylvania

7.a. CHANGE IN ACTIVE OTHER SUPPORT OF THE PI / SENIOR PERSONNEL

Nothing to report.

7.b. OTHER ORGANIZATIONS INVOLVED AS PARTNERS

Organization name: University of Pennsylvania

Location of Organization: Philadelphia, PA

Partner's Contribution to the Project: In-kind support (computers and equipment), pathology core facilities, and collaboration.

8. Special Reporting Requirements

Nothing to report

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9. Appendices

Appendix 1 -- Abstracts

Modification of Obesity Effects on Prostate Cancer Outcomes by Age and Education

C. Zeigler-Johnson¹, K. Morales², J. Mitchell², E. Spangler², K. Glanz², T. Rebbeck²

Thomas Jefferson University¹, University of Pennsylvania², Philadelphia, PA

Background: Poor prostate cancer (PCa) outcomes have been associated with obesity. Patient age and educational attainment may influence factors related to cancer knowledge, fear of cancer, and screening practices. The goal of this project was to determine how obesity effects on prostate cancer outcomes may be modified by age and education. The specific study aim was to examine the impact of education and age on the relationship between pre-treatment obesity and prostate cancer severity and risk of biochemical failure. The hypothesis was that the relationship between obesity and prostate cancer severity varies by demographic factors.

Methods: Our sample included 1318 Caucasian (CA) and 327 African American (AF) PCa patients in the Study for Clinical Outcomes Risk and Ethnicity at the University of Pennsylvania Health System. Obese was defined as a BMI of 30 kg/m². Patient age was dichotomized at the median (60 years) and education was quantified as less than college degree vs. college degree. The outcomes of interest were advanced stage (T3, T4), advanced grade (Gleason score 7+) and risk of biochemical failure. Modification by age and education groups was analyzed in age-adjusted and race-stratified logistic models for stage and grade outcomes and Cox regression models for time to biochemical failure.

Results: Obese CA men were more likely to have high PCa stage (OR= 1.61, 95% CI=1.22-2.11) and grade (OR=1.63, 95% CI=1.27-2.09). Effects on stage were similar regardless of age group or educational attainment. However, younger CA and AF men (OR=1.94, 95% CI=1.35-2.78 and OR=2.29, 95% CI=1.19-4.42, respectively), as well as CA men with higher education (OR=2.01, 95% CI=1.46-2.70) were more likely to have advanced grade at diagnosis. Time to biochemical failure was significant only among African Americans in the younger age group (HR=3.72, 95%CI=1.23-11.23) and with less education (HR=3.39, 95% CI=1.36-8.43).

Conclusions: The results suggested that obesity effects on PCa outcomes can be modified by patient age and education and should be studied in the context of these factors. Inconsistent obesity-PCa associations among studies may be related to varying sample population characteristics. Identifying key factors that influence obesity associations will provide critical information about patients whose PCa risks may decrease from targeted interventions. This research may suggest new approaches for prostate cancer intervention via weight management, physical activity, and targeted education, screening and treatment for those patients at highest risk for unfavorable outcomes and related mortality.

SES Discordance and Prostate Cancer Risk Factors

C. Zeigler-Johnson¹, K. Morales², K. Glanz², E. Spangler², J. Mitchell², T. Rebbeck²

Thomas Jefferson University¹, University of Pennsylvania², Philadelphia, PA

Focus Area: Social Determinants of Prostate Health Disparities

Background: It is unclear how patient and neighborhood socioeconomic status (SES) combine to impact prostate cancer (PCa) severity and risk factors. We studied concordant and discordant patient-neighborhood SES in PCa patients. Our aim was to examine risk factors for advanced PCa and test their association with SES concordance/discordance.

Methods: Our sample included 910 Caucasian (CA) and 146 African American (AF) PCa patients in the Study for Clinical Outcomes Risk and Ethnicity at the University of Pennsylvania Health System. We used patient level education and neighborhood level education (median percent of neighborhood residents with college education, using 2000 U.S. Census data) as markers for SES. Educational concordance/discordance for a patient was defined as (1) low patient education (<4y college) and low “neighborhood” education (<35% college educated neighborhood); (2) low patient education and high “neighborhood” education (≥35% college educated neighborhood); (3) high patient education (≥4y college) and low “neighborhood” education; and (4) high patient education and high “neighborhood” education. Age- and race-adjusted multinomial logistic regression models were used to examine risk factor relationships to concordance/discordance groups.

Results: Compared to the high-high concordant group, obese and AF men were more likely to be in the low-low concordant (obesity: OR=2.08, 95%CI=1.40-3.08; AF: OR=6.84, 95% CI=3.60-12.99) and high-low discordant groups (obesity: OR=1.83, 95%CI=1.25-2.66; AF: OR=3.18, 95%CI=1.59-6.36).

Conclusions: Obesity and AF were more prevalent in lower educated “neighborhoods” with no differential impact from patient-level education. Strategies to decrease prostate cancer risk for progression among patients living in lower SES neighborhoods may include reduction of obesity.

Diabetes and Prostate Cancer (CaP): Clinical Characteristics and Disparity in Outcomes

Elaine Spangler¹, Charnita Zeigler-Johnson², Jonathan Mitchell¹, Timothy Rebbeck¹

¹Univ. of Pennsylvania School of Medicine, Philadelphia, PA; ²Kimmel Cancer Center, Jefferson Medical College, Philadelphia, PA

Introduction: Disparities in prostate cancer (CaP) outcomes are poorly understood, but are likely caused by multiple factors. The presence of comorbidities may contribute to disparate outcomes in at least two ways: by altering the biological course of disease, and by influencing overall survival probabilities that impact treatment decisions. Diabetes has been associated with CaP in a variety of settings, and there is evidence that AA men suffer from diabetes at a higher rate than men of other races. We examined whether presence of diabetes is related to prostate cancer recurrence measured by post-prostatectomy biochemical (PSA) failure (BF).

Materials and methods: A prospective cohort of 554 European Americans (EA) and 184 African American (AA) CaP cases from the University of Pennsylvania were studied. We performed survival analysis for BF to evaluate the effect of diabetes on using Cox proportional hazards models adjusting for age, race, obesity, and Kattan score. Median post-prostatectomy follow-up was 40 months.

Results: Prevalence of diabetes was 6.3% overall (12% in AA and 5% in EA, $p < 0.0001$). AA men were more likely to be obese than EA men (33% vs. 19%, $p = 0.001$). During post-prostatectomy follow-up, 52 (28%) AA and 187 (33%) EA men experienced BF; 47 (9%) diabetic men and 691 (5%) non-diabetic men experienced BF. Diabetic men were twice as likely to experience BF as men without diabetes (HR=2.2, 95% CI: 1.26-3.92). Diabetes had a significant effect in both EA (HR = 2.1, 95% CI: 1.02-4.37) and AA (HR = 3.4, 95% CI: 1.16-10.0).

Conclusions: Being diabetic at time of CaP diagnosis increased the risk of prostate cancer recurrence, even after accounting for obesity and age. This effect was significant for both AA and EA, but the effect of diabetes appeared to be greater in AA. Diabetes may be an important predictor of post-prostatectomy CaP outcomes.

Appendix 2 -- Publication

Individual- and neighborhood-level education influences the effect of obesity on prostate cancer treatment failure after prostatectomy

Charnita Zeigler-Johnson¹ · Knashawn H. Morales² · Karen Glanz² · Elaine Spangler² · Jonathan Mitchell² · Timothy R. Rebbeck²

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Abstract

Purpose The relationship between obesity and prostate cancer (CaP) treatment failure is complex and may vary by patient- and neighborhood-level educational attainment. We evaluated whether patient- and neighborhood-level education is associated with the effect of obesity on biochemical recurrence.

Methods Seven hundred and forty-six CaP cases were classified into four groups: Concordant Low–Low: less educated cases (≤ 4 years college) living in a less educated neighborhood (below-median proportion of college-educated residents; $n = 164$); Concordant High–High: highly educated cases (≥ 4 years college) living in a highly educated neighborhood (above-median proportion of college-educated residents; $n = 326$); Discordant Low–High: less educated cases living in a highly educated neighborhood

($n = 69$); and Discordant High–Low: highly educated cases living in a less educated neighborhood ($n = 187$). Cox regression models were used to examine associations between obesity and biochemical (PSA) failure after prostatectomy stratified by the concordant/discordant groups.

Results The association of obesity with biochemical failure varied significantly by educational concordance/discordance ($p = 0.007$). Obesity was associated with risk of biochemical failure for less educated cases residing in less educated neighborhoods (HR 3.72, 95 % CI 1.30–10.65). The relationship was not significant for other concordant/discordant groups.

Conclusions Obesity effects on CaP outcomes vary by multilevel educational discordance/concordance. Strategies to decrease prostate cancer risk of progression may focus on reduction in obesity, particularly for less educated cases residing in less educated neighborhoods.

✉ Charnita Zeigler-Johnson
charnita.zeigler-johnson@jefferson.edu

Knashawn H. Morales
knashawn@mail.med.upenn.edu

Karen Glanz
kglanz@upenn.edu

Elaine Spangler
espangle@mail.med.upenn.edu

Jonathan Mitchell
jmitch@mail.med.upenn.edu

Timothy R. Rebbeck
rebbeck@exchange.upenn.edu

Keywords Prostate cancer · Obesity · Education · Cross-level interaction · Neighborhood SES

Introduction

Prostate cancer is a major public health burden with few confirmed modifiable risk factors. Obesity, a potentially modifiable risk factor, increases the risk of advanced disease at diagnosis and treatment failure [1–5]. Obesity also varies by socioeconomic status (SES). Poorer neighborhoods are more likely to have higher levels of obesity [6, 7]. A relationship between obesity and poor prostate cancer outcomes and recurrence of prostate cancer has been supported by several reports [8–10]. However, the association between obesity and prostate cancer outcomes has been

¹ Division of Population Science, Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA, USA

² Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, USA

inconsistent [3, 9, 11–13]. Similarly, low neighborhood SES has been correlated with increasing disease rates and poorer health outcomes, including mortality [14–18].

It has been hypothesized that adverse health effects are related to living in a neighborhood with an SES that is discordant with one's own SES [19]. This phenomenon of SES discordance is also referred to as cross-level interaction [20]. Associations of SES discordance and health outcomes such as mortality, hospitalizations, and alcohol consumption have been reported [20–23]. Reasons for these effects might be that low-SES individuals in high-SES neighborhoods have limited access to resources or less opportunity to maintain healthy lifestyles [20]. Individuals living in SES-discordant situations may experience differences in cancer education, access to care, and feelings of relative deprivation and stress compared with those living in SES-concordant situations [20, 24].

The goal of this study was to describe educational discordance/concordance in a population of CaP cases and evaluate whether associations between obesity and CaP severity are influenced by educational discordance/concordance.

Methods

Study Sample

A prospective study design was used to examine the relationship between discordance in educational attainment at CaP diagnosis and biochemical failure after radical prostatectomy. European American (EA) and African-American (AA) CaP cases were recruited at the University of Pennsylvania Health System (UPHS, Philadelphia, PA) via the Study for Clinical Outcomes Risk and Ethnicity (SCORE). All cases seen in these clinics that were newly diagnosed within the previous 12 months with a histologically confirmed primary CaP at any stage and underwent prostatectomy for treatment of their cancer were eligible for participation in this study.

Informed consent was obtained from all individual participants included in the study under a protocol approved by the Institutional Review Board at the University of Pennsylvania. Case status was confirmed by medical records review using a standardized abstraction form. Men were excluded from this study if they reported having exposure to finasteride or dutasteride at any time prior to their CaP diagnosis, were diagnosed more than 12 months prior to the date of study ascertainment, or had ever been diagnosed with cancer at any site (except non-CaP skin cancer) other than their recently diagnosed CaP.

We used patient-level education obtained from questionnaire self-report. Patient-level education was defined as having attended <4 years or ≥ 4 years of college.

Residential addresses of cases were geo-coded to the census tract level with Geographic Information Systems (ArcGIS) technology [25]. We used census tract college education variables from the 2000 US Census to measure neighborhood educational attainment. The median cut-point (37 %) for “percent of census tract residents with college education” was determined for all cases combined. Because 68 % of the SCORE sample was college-educated, we used college as the cut-point for defining educational discordance. Therefore, we evaluated the cross-level effects of having a college education and residing in a higher or lower than average college-educated community. Educational concordance/discordance was defined as (1) less than 4 years of patient college education and residence in a neighborhood with below-median neighborhood college education attainment; (2) less than 4 years of patient college education and above-median neighborhood college education attainment; (3) four or more years of patient college education and below-median neighborhood college educational attainment; and (4) four or more years of patient college education and above-median neighborhood college education attainment. Groups 1 and 4 represent educationally “concordant groups,” while groups 2 and 3 represent educationally “discordant” groups.

Statistical analysis

Univariate analyses of patient characteristics were evaluated after stratifying on concordance/discordance groups and obesity status. Non-obese was defined as body mass index (BMI) $< 30 \text{ kg/m}^2$, and obese was defined as BMI $\geq 30 \text{ kg/m}^2$. Chi-square tests and Fisher's exact tests were used to compare discrete variables across obesity groups. Kruskal–Wallis tests were used to compare differences in medians of continuous variables across obesity groups. Patient characteristics measured at diagnosis included tumor grade, with low grade defined as tumor Gleason score of six or below and high grade defined as a tumor score of seven or greater; prostate-specific antigen (PSA), with low-PSA group defined as $< 10 \text{ ng/ml}$ and high-PSA group defined as PSA $\geq 10 \text{ ng/ml}$; and age group $<$ and ≥ 60 years.

The primary study outcome was biochemical failure after prostatectomy, defined as a PSA greater than or equal to 0.2 ng/dl after primary treatment. Cases were followed for a median 28 months (range = 2–168 months). Cox regression models were adjusted for census tract, tumor grade, PSA at diagnosis, patient race, age, and the obesity–educational concordance/discordance interaction term. Modification of the association between obesity and biochemical failure by education was assessed by an interaction term in the Cox regression model.

Results

We studied 227 obese and 519 non-obese incident CaP cases recruited into the SCORE study from 1995 to 2011 and followed for biochemical failure after treatment (radical prostatectomy and radiation) for CaP in the UPHS. Cases ranged in age from 39 to 79 years ($SD = 6.54$). Thirty percent of SCORE cases were obese (Table 1). Sixty-nine percent of SCORE cases were college-educated (71 % non-obese and 63 % obese, $p = 0.024$). As shown in Table 1, the distribution of obesity was significantly different across the concordant/discordant groups ($\chi^2_3 = 15.314$, $p = 0.002$).

Among all cases, obese men were more likely than non-obese men to be AA (20 vs. 11 %, $p = 0.002$), less likely to have a college education (63 vs. 71 %, $p = 0.024$), presented with higher BMI (26.5 vs. 32.5 kg/m², $p < 0.001$) and lower PSA (4.9 vs. 5.3 ng/ml), and more likely to have higher tumor stage (35 vs. 24 %, $p = 0.003$) and grade (55 vs. 45 %, $p = 0.004$) at CaP diagnosis (Table 1).

Similarly, in stratified analyses, obese cases in the concordant high patient, high neighborhood education group were more likely to be AA ($p = 0.043$) and have lower PSA levels ($p = 0.044$). Obese cases in the discordant high patient, low neighborhood education group also were more likely to be African-American ($p = 0.016$) and have a high tumor grade ($p < 0.001$). BMI was consistently different by obesity status across each of the education concordance/discordance groups ($p < 0.001$).

Obese and non-obese cases in the concordant low patient, low neighborhood education group and the discordant low patient, high neighborhood education group did not differ in other demographic and clinical characteristics.

Overall, 78 (10.5 %) patients experienced biochemical failure during the study. Univariately, there were no differences in overall failure rates by obesity status ($p = 0.068$) or concordance/discordance groups ($p = 0.827$). However, obese cases in each concordant/discordant education group experienced a quicker time to biochemical failure (CaP recurrence) than non-obese cases (Fig. 1a–d). In multivariable models, the association of obesity with biochemical failure varied significantly by educational concordance/discordance ($p = 0.007$). Obesity was significantly associated with risk of biochemical failure in the concordant low patient, low neighborhood education group (HR 3.72, 95 % CI 1.30–10.65, Table 2). The HR was similar for the discordant low patient, high neighborhood education group, but the effect was not significant (HR 3.98, 95 % CI 0.60–26.54).

Discussion

Our results suggest that cases of lower education living in concordant lower education neighborhoods are at the highest risk of biochemical failure if they are obese. Elevated BMI previously has been associated with increased risk of biochemical failure [1, 9, 10, 26]. While the literature on SES discordance suggests that low-SES individuals living in high-SES neighborhoods may be at greatest risk of poor health outcomes or mortality, our results of a hospital-based CaP sample show that only obese cases living in a concordant low patient–low neighborhood education context are at particular risk of biochemical failure.

We hypothesize that obese low-education individuals living in low-education neighborhoods may experience “double jeopardy” because they are predisposed to multiple disadvantages at both the individual and neighborhood levels [22]. For CaP, living in education discordant or concordant high education contexts may neutralize risk of biochemical failure in obese cases. Similarly, either higher patient or neighborhood education may buffer risks that may impact poor CaP outcomes.

Several studies have examined SES cross-level effects on various health outcomes. Most have suggested that SES discordance resulted in worse health outcomes. Winkleby et al. [20] reported relationships between SES discordance and overall mortality. Death rates among low-SES men and women were highest in high-SES neighborhoods, lower in moderate-SES neighborhoods, and lowest in low-SES neighborhoods. Taylor et al. [21] extended this work to find similar associations for SES discordance. Higher hospitalization rates were observed among low-SES cases living in high-SES neighborhoods. Mulia et al. [22] reported relationships between SES discordance and high alcohol consumption, also among low-SES individuals residing in high-SES neighborhoods. Similar to our findings with biochemical failure, in a study of breast cancer cases, women with concordant low patient education and low neighborhood SES were determined to have worse all-cause survival than concordant high-SES women [23]. However, the risk was also higher among discordant SES groups (high education and low neighborhood SES) if the cases were AA or Asian American. Our study is the first to examine cross-level effects of education and obesity on CaP outcomes. While other studies defined patient-level SES as education with or without income and defined neighborhood SES as a composite variable to examine cross-level effects, we focused on education discordance because of limited income data at the patient level and the fact that education may be the most valid SES factor for this patient population.

Table 1 Education discordance groups (patient education–neighborhood education): demographics ($n = 746$)

Group	Patient characteristics	Total sample $n = 746$	Non-obese $n = 519$ (69.6 %)	Obese $n = 227$ (30.4 %)	p value for non-obese–obese comparisons
All SCORE prostate cancer cases	Median age (year)	59	59	58	0.268
	% Married	645 (86.7)	454 (87.8)	191 (84.1)	0.174
	% African-American	104 (13.9)	59 (11.4)	45 (19.8)	0.002
	% College Education	513 (68.8)	370 (71.3)	143 (63.0)	0.024
	% Ever smokers	375 (50.4)	260 (50.2)	115 (50.9)	0.862
	Median BMI (kg/m ²)	27.9	26.5	32.5	<0.001
	Median PSA ng/ml	5.2	5.3	4.9	0.006
	% PSA > 10 ng/ml	83 (11.3)	64 (12.5)	19 (8.4)	0.109
	% High stage (T3, T4)	202 (27.2)	124 (24.0)	78 (34.5)	0.003
	% High grade (7+)	348 (46.7)	224 (43.2)	124 (54.6)	0.004
		Total $n = 164$	Non-obese $n = 101$ (61.6 %)	Obese $n = 63$ (38.4 %)	p value for non-obese–obese comparisons
Concordant Low–Low	Median age (year)	58	58	59	0.626
	% Married	137 (83.5)	84 (83.2)	53 (84.1)	0.174
	% African-American	44 (26.8)	26 (25.7)	18 (28.6)	0.691
	% Ever smokers	100 (61.0)	58 (57.4)	42 (66.7)	0.238
	Median BMI (kg/m ²)	28.6	26.5	32.1	<0.001
	Median PSA	5.1	5.4	4.8	0.168
	% PSA > 10 ng/ml at diagnosis	19 (11.7)	14 (14.1)	5 (7.9)	0.231
	% High stage (T3, T4)	49 (29.9)	25 (24.8)	24 (38.1)	0.069
	% High grade (7+)	82 (50.0)	51 (50.5)	31 (49.2)	0.872
		Total $n = 326$	Non-obese $n = 250$ (76.7 %)	Obese $n = 76$ (23.3 %)	p value for non-obese–obese comparisons
Concordant High–High	Median age (year)	60	60	59	0.199
	% Married	285 (87.4)	223 (89.2)	62 (81.6)	0.079
	% African-American	22 (6.8)	13 (5.2)	9 (11.8)	0.043
	% Ever smokers	147 (45.2)	118 (47.4)	29 (38.2)	0.157
	Median BMI (kg/m ²)	27.7	26.5	32.7	<0.001
	Median PSA ng/ml	5.3	5.4	5.0	0.044
	% PSA > 10 ng/ml	39 (12.1)	33 (13.4)	6 (8.0)	0.213
	% High stage (T3, T4)	84 (25.9)	59 (23.7)	25 (33.3)	0.095
	% High grade (7+)	153 (46.9)	112 (44.8)	41 (54.0)	0.162
		Total $n = 69$	Non-obese $n = 48$ (69.6 %)	Obese $n = 21$ (30.4 %)	p value for non-obese–obese comparisons
Discordant Low–High (patient level <neighborhood)	Median age (year)	58	58.5	57	0.734
	% Married	63 (94.0)	42 (91.3)	21 (100.0)	0.301*
	% African-American	7 (10.1)	6 (12.5)	1 (4.8)	0.427
	% Ever smokers	46 (66.7)	30 (62.5)	16 (76.2)	0.267
	Median BMI (kg/m ²)	27.3	26.4	33.1	<0.001
	Median PSA ng/ml	5.1	5.1	5.6	0.809
	% PSA > 10 ng/ml	9 (11.8)	4 (8.3)	4 (20.0)	0.221*
	% High stage (T3, T4)	19 (27.5)	13 (27.1)	6 (28.6)	0.899
	% High grade (7+)	33 (47.8)	21 (43.8)	12 (57.1)	0.305

Table 1 continued

		Total <i>n</i> = 187	Non-obese <i>n</i> = 120 (64.2 %)	Obese <i>n</i> = 67 (35.8 %)	<i>p</i> value for non-obese–obese comparisons
Discordant High–Low (patient level >neighborhood)	Median age (year)	58	58	58	0.825
	% Married	160 (85.6)	105 (87.5)	55 (82.1)	0.313
	% African-American	31 (16.6)	14 (11.7)	17 (25.4)	0.016
	% Ever smokers	82 (44.1)	54 (45.0)	28 (42.2)	0.735
	Median BMI (kg/m ²)	28.3	26.8	32.4	<0.001
	Median PSA ng/ml	5.0	5.1	4.9	0.196
	% PSA > 10 ng/ml	17 (9.2)	13 (11.0)	4 (6.0)	0.300
	% High stage (T3, T4)	50 (26.9)	27 (22.7)	23 (34.3)	0.086
	% High grade (7+)	80 (42.8)	40 (33.3)	40 (59.7)	<0.001

* *p* value based on Fisher's exact test when cells had sample size ≤ 5

Bold values indicate $p < 0.05$

We also examined the separate interactions of patient- and neighborhood-level education with obesity on biochemical failure. Although an increased risk for obese patients with low patient-level education was observed in those separate analyses, our study adds to the CaP literature the finding that the context in which high-risk patients live also matters. We found that only obese patients with low patient-level education living in low-education neighborhoods were at significantly increased risk of biochemical failure.

Obesity is a potentially modifiable risk factor for disease progression and poor outcomes for numerous diseases including prostate cancer. Obesity is believed to increase the risk of advanced tumor stage and grade at diagnosis, younger age at diagnosis, and biochemical failure (disease recurrence) after treatment [1–4]. However, the relationship between obesity and prostate cancer is complex. A recent large cohort study demonstrated that obesity was associated with a decreased risk of low-grade CaP but an increased risk of high-grade CaP [5]. While some previous studies did not support a relationship of obesity with CaP [3, 9, 11–13] or associations with some outcomes and not others [12], inconsistent findings may have been caused by differences in the composition of study populations, including the prevalence of obesity, ethnic distribution, nationality of the population, PSA screening recommendations in international studies, and diagnostic obstacles associated with obesity [3, 12, 27–31].

Both treatment effects and biological effects have been proposed as explanations for the effect of obesity on CaP outcomes [5, 32–35]. After prostatectomy, overweight and obese cases have significantly longer hospital stays compared with normal weight cases. Estimated blood loss during the procedure is also greater in obese and overweight cases [26]. However,

potency and continence rates after treatment are similar among weight groups, so technically inferior operations do not account fully for differences in treatment failure [26]. In addition to treatment effects, numerous biological pathways have been associated with dysregulation among obese individuals, including aberrant hormone production, hormone metabolism, and alterations in insulin, insulin-like growth factor 1 (IGF-1), and leptin are well established [36–38]. Obesity also appears to promote hyperandrogenicity and presents a chronic inflammatory environment that sets the stage for cancer progression and poor prognosis, although underlying mechanisms within the tumor are poorly understood [38–42].

We focused on education as a surrogate for SES in this study, but we realize that other neighborhood and patient characteristics may contribute to the associations that we observed. Education and income (and combined metrics including both) are commonly used in the USA as measures of patient- and neighborhood-level SES [20, 22, 23]. Education is readily available in research databases and has been used in other studies of cancer outcomes [23, 43]. Education is also important because it may correlate with knowledge, literacy, sense of empowerment, and skill sets that may be needed to navigate health care, decision making, and coping with disease. Although patient education is not an optimal proxy for individual SES (i.e., the same educational attainment does not result in the same societal advantage for all people or cultures), it is perhaps the best indicator to use in a population of aging men [43]. Many older men live on fixed incomes that are not reflective of their SES or accumulated wealth. Also, poor health may decrease income, but will not alter educational attainment [44]. Unlike income and occupation, educational attainment is often fixed early in

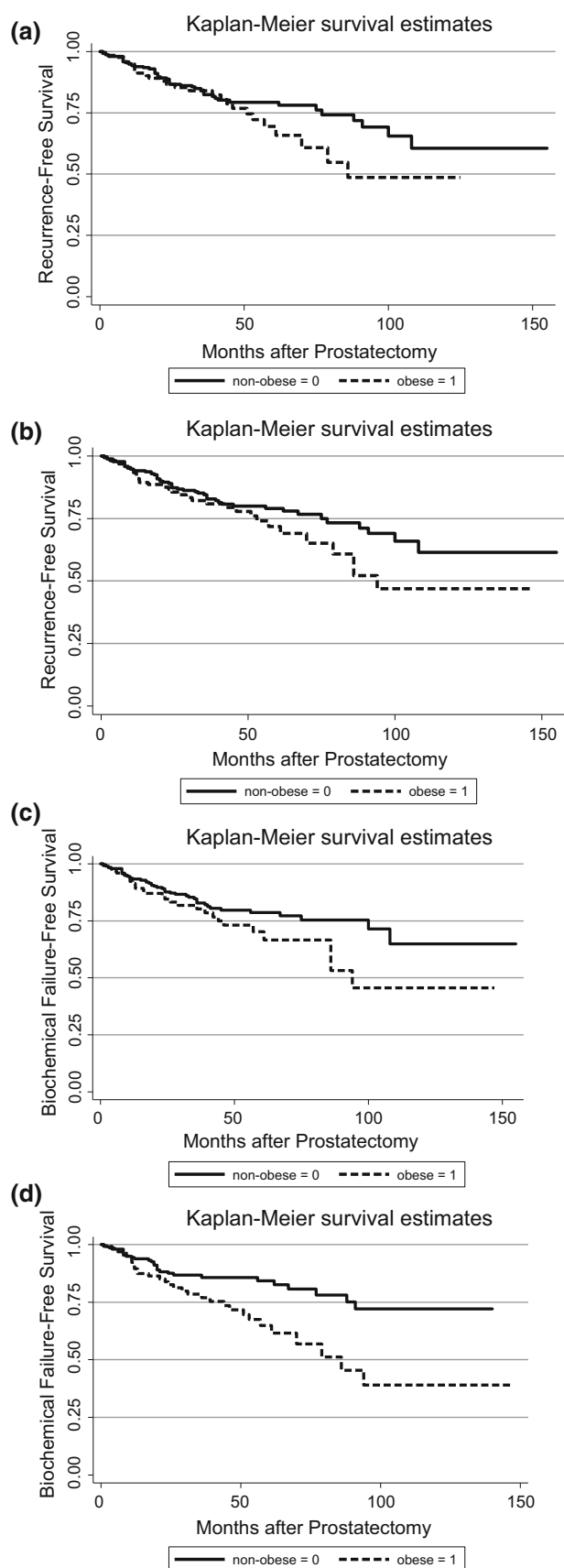


Fig. 1 **a** Time to biochemical failure (Recurrence) by obesity: lower patient education, lower neighborhood education. **b** Time to biochemical failure (recurrence) by obesity: lower patient education, higher neighborhood education. **c** Time to biochemical failure (recurrence) by obesity: higher patient education, lower neighborhood education. **d** Time to biochemical failure (recurrence) by obesity: higher patient education, higher neighborhood education

adulthood and is less likely than income to be affected by factors such as illness, change in job, or retirement [22]. Education is also predictive of having a more favorable occupation, income, or neighborhood.

Disease risks at the individual and neighborhood level often are impacted by education. According to SEER data, higher educational attainment has been associated with greater risk of prostate and breast cancers alike. Compared to college-educated men, men with less than a college education were 0.79 as likely to be diagnosed with prostate cancer [45]. Prostate screening (and therefore CaP incidence) is more common in men with higher education, white-collar jobs, access to good health care, urban residences, and higher household income [46]. Neighborhood-level education also predicts metabolic syndrome independently of individual-level SES [47].

A number of limitations affect the inferences of this study. We were unable to determine length of time at reported residence and thus cannot evaluate duration of neighborhood “exposure.” We do not know when neighborhood factors are most likely to contribute to cancer outcomes [43], nor do we know much what period of time is required for a particular neighborhood exposure to affect the biology of disease [48]. We began our investigation at the point of CaP diagnosis. This allowed us to evaluate education consistently in all cases. Another limitation of our study is the fact that the cut-points between more and less advantaged neighborhoods are arbitrary and are dependent upon our sample characteristics. We may also be limited by the “intersection of racial and SES segregation,” in which relatively few AA live in the least deprived areas and few EAs live in the most deprived areas [49]. Thus, study participants are not randomly allocated into census tracts. However, we adjusted for race, age, and census tract in multivariable analysis. We also were not able to detect effects for the group that may be at highest risk: low-SES individuals residing in high-SES neighborhoods. As in other studies, this category was represented by the smallest sample size [22].

The present was ascertained from a tertiary care center, so the external validity of the results may be limited to similar hospital settings. Some cases travel from long distances to receive treatment, which means that this is also a patient group that is educated about healthcare options and has ability to travel for health care. This is also a group that tends to have medical insurance or other means of financing care. Our sample was primarily comprised of low-stage CaP cases (75 %) and was more educated than

Table 2 SCORE models: relationship between obesity and prostate cancer outcomes by college concordance/discordance (patient college–neighborhood college)

Concordance/discordance group	HR for the effect of obesity on biochemical failure (95 % CI)
Concordant—Low–Low	3.72 (1.30–10.65)
Discordant—patient level < neighborhood	3.98 (0.60–26.54)
Discordant—patient level > neighborhood	1.06 (0.43–2.62)
Concordant—High–High	0.52 (0.17–1.59)

Cox models adjusted for census tract, tumor grade, PSA at diagnosis, patient race, age, and obesity–college concordance/discordance interaction

Bold values indicate $p < 0.05$

the general US population (68 % of our sample had a bachelor's degree, and our median for percent of college-educated residents in the surveyed census tracts was 37 vs. 29 % of the US male population with college degrees). Replication studies with diverse patient populations will add external validity to the results of this study.

We chose to use census tracts as our “neighborhood” variable for this study. Although we could have used other administrative units (census blocks or zip codes), we used the most commonly utilized unit of analysis to increase comparability with other studies. Census tract boundaries are intended to combine individuals that tend to be similar with regard to social and economic characteristics. Census tracts are one of the preferred area-based units to use when attempting to capture economic deprivation. They are meaningful across regions and over time and easily understood/defined [25, 50]. Future studies may examine how cross-level effects vary by administrative unit.

Conclusions

The effects of neighborhood characteristics on the health of older men have been poorly studied. This project identified CaP cases and communities at highest risk of obesity, advanced cancer and poor treatment outcomes. Obese men are a high-risk group for poor prostate cancer outcomes, but not all obese men carry the same risk. Eliminating CaP disparities requires enhanced efforts to identify highest risk individuals. Empowering disadvantaged communities to improve aspects of the physical or social environment may be an intervention that can benefit the health of residents for years to come. While the present study does not address the mechanisms underlying the association between obesity and prostate cancer aggressiveness, research involving obese prostate cancer cases may suggest new approaches for prostate cancer intervention via weight management,

physical activity, targeted screening, CaP education, and novel treatments.

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Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no conflict of interest.

Research Involvement of Human Participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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